Amendments to the Claims:

All amendments and cancellations to the claims are made without prejudice or disclaimer. This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Cancelled)

2. (Cancelled)

3. (Previously Presented) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

providing an ensemble of related protein backbone structures;

selecting a plurality of variable positions in said ensemble of related protein backbone structures;

selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures;

generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

generating a combinatorial library of proteins from said probability matrix; and

generating an output of the combinatorial library.

4. (Currently amended) A method according to claim 3 wherein the ~~said~~ steps of selecting a plurality of variable positions, selecting a set of amino acids, applying, sampling and evaluating are repeated more than once to generate said probability matrix.

5. (Previously Presented) A method according to claim 3 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

6. (Previously Presented) A method according to claim 3 wherein at least one backbone structure of the ensemble is derived from the structure of a natural protein.

7. (Previously Presented) A method according to claim 3 wherein at least one backbone structure of the ensemble is generated by comparative modeling.

8-13. (cancelled)

14. (Previously Presented) A method according to claim 3 wherein said ensemble of related backbone structures comprises backbone structures of a family of natural proteins.

15. (Previously Presented) A method according to claim 3 wherein said ensemble of related backbone structures is derived from an NMR structure.

16. (Previously Presented) A method according to claim 3 wherein said ensemble of related protein backbone structures is generated by a Monte Carlo simulation.

17. (Previously Presented) A method according to claim 3 wherein said ensemble of related protein backbone structures is generated by a molecular dynamics simulation.

18. (Currently amended) A method according to claim 3 further comprising combining ~~wherein~~ the information from at least two probability matrices ~~is combined~~ to satisfy at least two constraints on sequence space.

19 - 37. (cancelled)

38. (Currently Amended) A method according claim [[2]] 3 that comprises selecting said variant protein ~~wherein the amino acid~~ sequences ~~of the at least one protein sequence is selected~~ for the combinatorial library of proteins by identifying the amino acid with the lowest free energy at each position from the probability matrix.

39. (Currently amended) A method according claim 3 ~~further comprising~~ wherein the step of evaluating energetic fitness comprises selecting an upper limit on free energy, and the step of generating said probability matrix comprises allowing amino acid variations among amino acids that are below the upper free energy limit~~, and generating the combinatorial library of protein sequences from said probability matrix~~.

40. (Currently amended) A method according claim 3 further comprising incorporating amino acids in the probability matrix generating step at incrementally lower probabilities until a desired complexity is achieved in the probability matrix, and generating a ~~library of protein sequences~~ said combinatorial library of proteins from said probability matrix.

41. (Previously Presented ) A method according to claim 18 wherein the at least two constraints comprise a first constraint corresponding to a first structural form and second constraint corresponding to a second structural form that is distinct from the first structural form.

42. (Currently Amended) A method according to claim 18 ~~wherein~~ comprising combining the at least two probability matrices ~~are combined~~ by adding or subtracting free energies values from said probability matrices.

43. (Currently Amended) A method according to claim 18 wherein the ~~combining process is iterated~~ step of combining information is repeated.

44. (Currently Amended) ~~The~~ A method of claim 3 wherein the sampling an amino acid position comprises freezing side chain identities and rotamers at positions in the protein other than the sampled amino acid position.

45. (Currently amended) ~~The~~ A method ~~of~~ according to claim 3 ~~wherein~~ further comprising expressing the probability matrix ~~is expressed~~ as a set of partition functions.

46. (Currently amended) ~~The~~ A method ~~of~~ according to claim 3 ~~wherein~~ further comprising expressing the probability matrix ~~is expressed~~ as a free energy value.

47. (Currently Amended) ~~The~~ A method ~~of~~ according to claim [[1]] 3 wherein the probability matrix comprises information for all twenty amino acids.

48. (Currently amended) ~~The~~ A method ~~of~~ according to claim 61 further comprising screening or selecting one or more proteins from the library of proteins for a desired property.

49. (Currently Amended) ~~The~~ A method ~~of~~ according to claim 4 ~~wherein,~~ comprising in a subsequent repeat, ~~cycle, the protein design algorithm uses~~ using the probability matrix from a previous ~~cycle~~ repeat.

50. (Currently Amended) The method of claim 48 wherein the screening or selecting one or more proteins from the library of proteins comprises identifying a protein with enhanced catalytic activity or altered specificity, relative to an initial protein whose backbone structure is one of the backbone structures of the ensemble.

51-60. (cancelled)

61. (Previously Presented) A method of providing a protein library, the method comprising:

providing an ensemble of related protein backbone structures;

selecting a plurality of variable positions in said ensemble of related protein backbone structures;

selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures;

generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in

said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

producing a library of proteins that include proteins that each comprise a sequence based on said probability matrix.

62- 66. (Cancelled)

67. (Currently Amended) ~~The~~ A method ~~of~~ according to claim 3 wherein the step of sampling and evaluating fitness of one or more amino acids comprises sampling and evaluating fitness of different rotamers of the one or more amino acids at position in at least one backbone structure.

68. (Cancelled)